REMARKS

Claims 1-21 remain pending in the instant application. The Examiner has withdrawn claims 5,6,17 and 18 pursuant to 37 CFR 1.142(b) as being drawn to non-elected species, there being, no allowable generic or linking claim. Applicants have amended claims 1 and 13. Support for such amendments can be found throughout the specification. No new matter has been added. Applicants have also added new claims 22 and 23 with further recite the amelioration of symptoms of a (neurodegenerative) disorder. Applicants submit that the claims as amended are allowable. Claims 5-6 and 17-18 are therefore subject to reinstatement, claims 1 and 13, being generic for the elected species.

The Invention

The claimed invention generally relates to methods for altering expression of a glutamic acid decarboxylase (GAD) in a region of the brain. More specifically, the claims as amended, relate to methods of altering the level of GAD_{65} in the central nervous system of a subject that requires such modification. This is accomplished by identifying a target site in the central nervous system that requires modification and delivering a vector that comprises a nucleic acid sequence encoding glutamic acid decarboxylase (GAD) to a target site of the central nervous system (e.g., a region of the brain), to alter expression of GAD in the region of the brain.

More specifically, the present application also discloses and claims a method of treating a disease by delivering a vector that comprises a nucleic acid sequence encoding glutamic acid decarboxylase 65 (GAD65) to target cells of the central nervous system (e.g., a region of the brain), to treat or reduce a neurodegenerative disease. Applicants have discovered that increased levels of GAD can ameliorate certain central nervous system (CNS) diseases, and that gene therapy can be used effectively to increase GAD in the central nervous system.

In support of this application, Applicants hereby re-submit the Rule 132 Declaration of Dr. Michael Kaplitt (hereinafter "Kaplitt Decl.") regarding the scope of the invention, originally submitted in the parent application App. Ser. No. 09/863,179. Applicants note that the additional experiments referred to in the Kaplitt Decl. appear in full form in U.S. Pub. No. 2005/0025746 (App. Ser. No. 10/802,497) (hereinafter "'746 Publication"), which is a continuation-in-part of the instant application.

Claim Objections

The Examiner objected to claims 1-4, 7-16 and 19-21 as being drawn to non-elected subject matter. Applicants submit that amended claims 1 and 13 are generic and allowable. As such the rejection should be withdrawn.

Double Patenting Rejection

The Examiner rejected to claims 1-4, 7-16 and 19-21 on the grounds of non-statutory obviousness type double patenting as being unpatentable over claims 1-14 of U.S. Patent 6,780,409. Applicants submit that they will file the appropriate terminal disclaimer once allowable subject matter is found.

Claim Rejection under 35 U.S.C. § 112 – Enablement

The Examiner has rejected claims 1-4, 7-16 and 19-21 under 35 U.S.C. § 112 , first paragraph for lack of enablement. In particular, the Office Action asserts that:

> [t]he specification, *while being enabling for a method of treating Parkinson's disease by administering to a region of the brain a vector comprising a nucleotide sequence a nucleotide sequence encoding glutamic acid decarboxylase (GAD)*, wherein the symptom of Parkinson's disease is ameliorated, *does not reasonably provide enablement for the use of any type of vector* for the treatment of Parkinson's disease, *nor any target tissue other than the brain*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims (emphasis added).

As supporting this ground for rejection, the Office Action cites certain references suggesting that gene therapy is an unpredictable art, and as such Applicants invention should be limited as stated above. Applicants disagree. Once Applicant's teachings with respect to GAD expression are known, the design of particular vectors and the selection of various CNS sites is clearly within the capabilities of one skilled in the art.

It is well established that enablement is not precluded by the need for experimentation, even a large quantity of experimentation, if the specification, in combination with the knowledge available in the art, provides guidance regarding how to carry out the experimentation such that the experimentation is not "undue." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (citing *In re Angstadt*, 537 F.2d 489, 502-504, 190 USPQ 214, 218 (CCPA 1976)).

Furthermore, "(i)The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention *See Viviv Technologies, Inc. v. American Science and Engineering, Inc.* 200 F.3d 795, 804, 53 USPQ2d 1289, 1295 (Fed. Cir. 1999) ('Patents are written by and for the skilled artisans')." (2) "To hold otherwise would require every patent document to include a technical treatise for the unskilled reader. Although an accommodation to the 'common experience' of lay persons may be feasible, it is an unnecessary burden for inventors and has long been rejected as a requirement for patent disclosures. *See Atmel Corp.*, 198 F.3d at 1382, 53 USPQ2d at 1230 (Fed. Cir. 1999).

The Examiner is attempting to use this rejection to limit the scope of Applicant's claims to cover only the embodiment of the invention that is disclosed in the working examples. The specification of the present invention however provides adequate teaching and guidance to enable one of ordinary skill in the art to make and use the claimed methods of the present invention to treat neurodegenerative diseases using vectors carrying the GAD_{65} gene, and delivering these vectors to a region of the central nervous system that requires modification with the GAD_{65} gene. The claims clearly recite methods that are sufficiently enabled by the specification of the present invention. Accordingly, Applicant is entitled to a claim coverage for all subject matter that one of ordinary

skill in the art would gather from the teachings and guidance of Applicant's specification, as well as from the knowledge available in the art.

The working examples provided by the specification of the present invention are *merely illustrative* of the underlying inventive concept of Applicant's invention – they do *not* represent the sum total of Applicant's underlying inventive concept. Accordingly, the scope of Applicant's claimed methods should not be limited to only the use of the AAV vector or delivery to only the subthalmic nucleus, because Applicant has provided adequate disclosure for other suitable vectors that can be readily substituted into the methods disclosed by the present specification to deliver the GAD_{65} gene to any region of the brain, not just the subthalmic nucleus. Moreover, the working example demonstrates the proof-of-principle that GAD_{65} overexpression in a region of the brain associated with a neurodegenerative disease, such as Parkinson's disease, can help ameliorate the disease. The same methodology described in the application can readily be applied to other neurodegenerative diseases that require modification with GAD_{65}.

At the time the invention was filed (priority application was filed in May 2000), the knowledge available to the skilled artisan, was well established for treating neurodegenerative diseases such as Parkinson's disease with gene therapy. Thus, gene therapy for neurodegenerative diseases such as Parkinson's disease was not an unpredictable art. In fact, a number of representative articles are presented below demonstrating that the skilled artisan recognized, and used gene therapy as a means of treating neurodegenerative diseases. The skilled artisan has used a number of different vectors that deliver a particular desired gene, and express the protein in the desired location in the central nervous system. Moreover, the skilled artisan has successfully delivered the vectors to different regions of the brain associated with a neurodegenerative the disease.

Specifically, Applicants have shown that GAD_{65} gene transfer into glutamatergic excitatory neurons leads to an inhibitory bias with altered network activity. This phenotypic shift provides strong neuroprotection and demonstrates there is plasticity between excitatory and inhibitory

neurotransmission in the mammalian brain that results in a therapeutic effect, in particular the alleviation of symptoms of Parkinson's disease (Kaplitt Decl. para. 5-6).

The same inventive concept of delivering GAD to a region of the central nervous system, can be applied to any CNS disease in which increasing GABA production is desirable (Kaplitt Decl. para. 7). Applicants themselves **have used the method of the invention, to reduce the symptoms of epilepsy, by delivering GAD_{65} to a region of the brain involved in epilepsy**, e.g., the hippocampus. (Kaplitt Decl. para. 8-10; see also '746 Publication, para. [348] – [388] (Example 9)) . Other groups have used the vectors and/or methods of the application to target regions of the brain to address such other conditions such as metabolic disorders. (Kaplitt Decl. para. 11-12) and chronic pain (Kaplitt Decl. para 13-14).

The teaching of the application is not limited to the delivery methods of the examples. Other vectors, for example, may be used to target the CNS and alter GAD expression (Kaplitt Decl. para. 13-14)

Finally, it is obvious that GAD_{65} can be targeted specifically to different regions of the brain including the hippocampus (Kaplitt Decl. para. 8), the lateral nucleus of the hypothalamus (Kaplitt Decl. para. 12), the rostral agranular insular cortex (RAIC) (Kaplitt Decl. para. 14) and even the visual cortex (Kaplitt Decl. para. 16).

Thus one of ordinary skill in the art, would be able to use the application's disclosure, in addition to the knowledge available in the art, to apply the invention to alter expression of glutamic acid decarboxylase generallaly and GAD_{65} specifically in a selected region of the CNS. In summary, the disclosure in the application, in combination with the knowledge available in the art, would enable one skilled in the art to perform the full scope of the claimed invention without undue experimentation.

Claim Rejection – 35 USC § 103

Claims 1-3, 7-16 and 19-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Robert et al (1997, Gene Therapy 4: 1237-1245, cited on IDS filed 3/16/04). Alternatively the claims are also rejected under 35 U.S.C. § 103 over Robert et al in light of U.S. Pat. No, 6,180,613 to Kaplitt et al. (filed June 6, 1995).

Amended claims 1-4 and 7-12 are drawn to a method of altering expression of glutamic acid decarbocylase 65 *(GAD$_{65}$)* in a region of the CNS of a subject comprising (i) identifying a target region *that requires modification*, (ii) delivering a vector comprising a nucleotide sequenced encoding GAD$_{65}$ into said target region; and (iii) expressing GAD in the target region.

Amended claims 13-16 and 19-21 are directed to a method of altering expression of GAD$_{65}$ in a region of the CNS of a subject having a disorder which causes morphological and/or functional abnormality of a neural cell or population of neural cells comprising (i) identifying a target region *that requires modification*, (ii) delivering a vector comprising a nucleotide sequenced encoding GAD$_{65}$ into said target region; and (iii) expressing GAD in the target region.

New claims 22 and 23 with further recite the amelioration of symptoms of a (neurodegenerative) disorder.

Roberts et al. discloses the administration of a rat GAD$_{67}$ gene under the control of the Rous sarcoma virus long terminal repeat promoter is able to express the transgene in primary culture of neurons and glial cells. The virally encoded GAD$_{67}$ was also found to be expressed in a "few cells in a small volume around the injection site" (Roberts et al, p. 1240).

Roberts et al, neither anticipates nor renders obvious the amended claims. As mentioned above Claims 1-4 and 7-12 are drawn to a method of altering expression of glutamic acid decarbocylase 65 *(GAD$_{65}$)* in a region of the CNS of a subject comprising (i) identifying a target region *that requires modification*, (ii) delivering a vector comprising a nucleotide sequenced encoding GAD$_{65}$ into said target region; and (iii) expressing GAD$_{65}$ in the target region. Roberts

does not teach (a) method of altering expression of GAD_{65} in a subjected; (b) identifying a target site that requires GAD_{65} modification ; and (c) expressing GAD_{65} in said target region.

Claims 13-16 and 19-21 are further directed to a method of altering expression of GAD_{65} in a region of the CNS of a subject *having a disorder which causes morphological and/or functional abnormality of a neural cell or population of neural cells.* Roberts does not teach the administration of GAD_{65} to such a subject.

In fact, Robert et al. only implicates GAD_{67} as having a role in CNS disorders and specifically *teaches away* from the administration of GAD_{65} in such instances. Robert et al. specifically states that "GAD67 was chosen instead of GAD65 because it is the active (holoenzyme) form" (Robert p. 1241). In fact, according to Robert, the presence of a high level of GAD_{67} (but not GAD_{65}) mRNA were found in hippocampal granule cells in rats in kainic acid models of epilepsy. This fact argued against GAD_{65}'s implication in neurodegenerative diseases generally and epilepsy specifically and led to Robert et al to investigate the possibility of delivering GAD_{67} to neural cells (*See* Robert et al. pp 1237-1238).

Applicants, in contrast, have found that GAD_{65} is equally if not more effective in treating neurodegenerative diseases that implicate GABA. (*See. e.g.*, Example 6 of the instant application wherein GAD_{65} administration showed a better protective effect in apomorphine-induced rotational asymmetries as compared to GAD_{67}; *see also,* Example 9 *of* '746 publication where in a kainic acid model of epilepsy in rats, GAD_{65} rats had significantly less bilateral forelimb clonus than rats given GAD_{67} gene therapy).

The addition of Kaplitt et al (U.S. Pat. No. 6,180,613) does not remedy any of the deficiencies of Robert et al. The Examiner cites Kaplitt et al for the proposition that one of ordinary skill in the art would clearly have desired to transfect non-dividing cells of the brain and that one of skill in the art would have been motivated to use AAV vectors instead of adenovirus vectors in the method disclosed by Robert. This does not remedy the deficiencies of Robert et al.. The claims require the *identification of a target site in the CNS that requires modification and administering* GAD_{65}. According to Robert, the only effective modification of a target site

that one of ordinary skill in the rat would make would be through the administration of GAD_{67} because GAD_{67} was considered at the time *"the active form when linked to pyridoxal phosphate" (Robert p. 1238).*

In summary, at the time, one would have only thought of administering GAD_{67} and not GAD_{65} to a target region of the brain of a subject having a neurological disorder in order to ameliorate such a disorder. As such, the claims as they stand cannot be deemed obvious in light of the cited art.

Conclusion

Applicants believe that all pending claims are allowable for the reasons stated above. Applicants invite the Examiner to call the undersigned attorney if there are any further questions and to speed prosecution.

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Respectfully submitted,

By_____

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